Remanufacture of Adenovirus Vaccines Type 4 and 7

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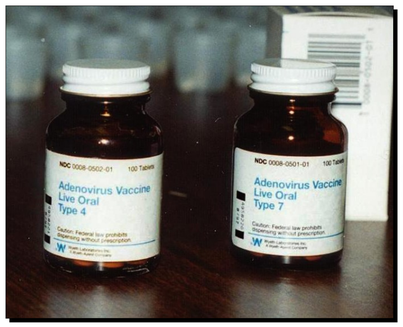


Abstract

Background:
Prior to the use of vaccines, adenovirus (Adv) serotypes 4 and 7 accounted for 60% of all acute respiratory disease (ARD) in recruits who were hospitalized. The clinical studies that lead to the U.S. Food and Drug Administration (FDA) approving Adv were co-sponsored by the Army and the National Institute of Allergy and Infectious Diseases. Wyeth Laboratories produced enteric-coated tablets containing live adenoviruses type 4 or 7 exclusively for the military from 1980 to 1996. In 1984 Wyeth Laboratories notified the Defense Supply Center Philadelphia (DSCP) that the FDA required a new facility to manufacture Adv that a facility could not be built without additional funds. Since the funds were unavailable at that time, Wyeth was forced to ended vaccine production in 1996. The last of the stocks of the vaccines were depleted in 1999.

Current Situation:
Since 1999, approximately 10%-12% of all recruits have become ill with adenovirus infection in basic training, similar to the pre-vaccine era. There were two deaths of Navy recruits in July and September 2000 at Great Lakes, Illinois from suspected adenovirus infections.

Award of Contract:
A contract to remanufacture the type 4 and 7 adenovirus vaccine was awarded to Barr Laboratories, Inc. on 25 Sep 2001. The first phase requires an Investigational New Drug (IND) application and successful completion of phase 1 clinical trials. The second phase requires completion of all clinical trials and full FDA licensure of the product. The vaccines are expected to be available in 2008.

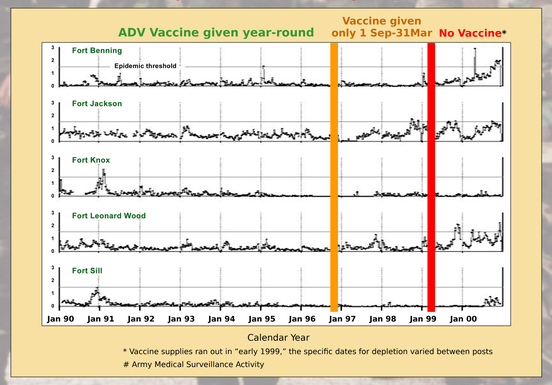
Background

- Prior to the introduction of adenovirus vaccines in 1971, up to 80% of recruits developed adenovirus infections, 20% were hospitalized, and a small number died.
- Out of several virus serotypes, adenovirus Types 4 and 7 accounted for the majority of hospitalized recruits.
- Protective vaccines were fielded in 1971, and used for Army, Navy, and Marine Corps recruits. These vaccines virtually eliminated adenovirus disease from basic training centers since they protected recruits from the most common strains, Type 4 and Type 7.
- The sole producer of adenovirus vaccines (Wyeth Laboratories) ceased vaccine production in 1996. All adenovirus vaccine stocks were depleted in 1999.

Timeline: 1955-2001

- 1955: Adv type 3,4,7 shown to be most important cause of ARDs for military recruits, particularly type 4
- 1957: First Adv vaccines produced and tested in a small trial
- 1964-69: Field trials of Adv vaccine in military recruits
- 1971: Administration of Adv vaccine 4 and 7 to recruits
- 1980 FDA approves Wyeth's application to manufacture Adv
- 1984 Wyeth advises DSCP that to meet new FDA requirements a new facility is need to manufacture the vaccines
- 1985 Wyeth advises DSCP that they will make the vaccine on a year-to-year basis
- 1985 DSCP seeks other manufacturers, but none are interested
- 1994 Wyeth informs DSCP that they would no longer manufacture Adv
- 1996 Wyeth met with ASD(HA) and Greer to discuss the possibility of a technology transfer
- 1996 DSCP issues solicitation for a contract to produce adenovirus vaccine with only Greer submitting a proposal
- 1996: Last shipments of Adv to DoD
- 1997 Meeting of FDA, DoD, DSCP,Wyeth and Greer to facilitate the transfer of the Wyeth production capability to Greer
- 1997 Greer rescinds all earlier offers for the production of Adv
- 1999: Vaccine supplies depleted
- 2001: Contract signed for Barr Laboratories to produce vaccines. Vaccines not expected for 5-7+ years.

Historical ARD rates by week for Army Basic Training: 90'-00' (Source: AMSA#)
(cases per 100 trainees per week)



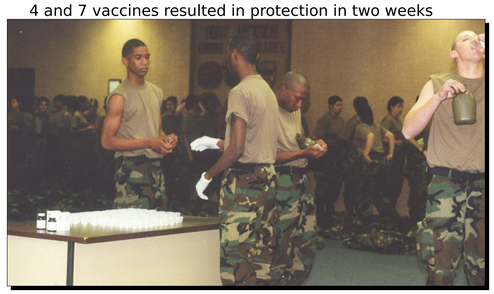
* Vaccine supplies ran out in "early 1999," the specific dates for depletion varied between posts
\# Army Medical Surveillance Activity

Current Situation

- Comparing Calendar Year 2001 with 2000, there was a 36% increase ARD cases among Army trainees (14,894 cases). Based on 1996-1998 data, approx. 30-60% of these ARD cases were adenovirus types 4 and 7 (4468-8936 cases of either Adv type 4 or 7).
  - Source of Data:: Army Medical Surveillance Activity, Gray et. al., Clin Infec Dis 2000:31:663-70

The Vaccine: Types 4 and 7

- Orally administered, enteric-coated live vaccine
- There were no adverse reactions reported from the hundreds of thousands of doses of Adv administered to military recruits
- The single-dose simultaneous administration of Types 4 and 7 vaccines resulted in protection in two weeks



Steps towards the current contract

- In 2000, the Institute of Medicine concluded that the $14 Million of the Defense Health Program for funding was insufficient to attract manufacturers.
- On 05 Jan 2001 a Request for Information entitled, "Re-establish the Manufacture of Adenovirus Vaccines, Types 4 and 7," was published in the Commerce Business Daily
- On 05 Mar 2001 a Request for Proposals was issued by USAMRMC for the re-manufacturer of Adv

Contract

- A $17.4 million, 3-year baseline contract was awarded in September 2001 to Barr Laboratories, Inc. for the remanufacture of Adenovirus vaccines Type 4 and 7. Upon the successful completion of the phase 1 trials, an option for $18 million will be approved to support phase 2 and 3 trials and FDA approval.
- The contract is administered by the U.S. Army Medical Research and Materiel Command (USAMRMC).
- Phase 2 and 3 clinical trials and US Food and Drug Administration approval are expected to be completed by the end of FY O6.
- Full rate of production quantities of vaccine are expected by the end of FY 07.

Statement of Work

- Barr will furnish the necessary personnel, expertise, materials, supplies, facilities, equipment, transportation, and travel required to obtain FDA approval. To get this approval Barr must
  1) Re-establish a manufacturing line for the production of Adv (Types 4 and 7)
  2) manufacture at least three consecutive releasable lots each of candidate adenovirus vaccines (Types 4 and 7),
  3) prepare human and animal protocols for evaluating the safety and immunogenicity of the candidate vaccines,
  4) conduct clinical trials to demonstrate candidate vaccines safety and immunogenicity individually and in combination, and
  5) file a Biologic License Application (BLA) with the FDA and get it approved
- The Army Office of the Surgeon General will sponsor the IND, but the FDA approved license for Adv will be held by Barr

Timeline for Production & Clinical Trials

- 2 years to develop manufacturing capability and produce 3 pilot lots (including one Current Good Manufacturing Practice (cGMP) lot) of each vaccine type and another 8-10 months conducting the Phase 1 clinical trial
- 8 months to manufacture the first consistency lots
- 8-10 months for the Phase 2 clinical trial
- 1 year to complete the Phase 3 clinical trial
- The second and third consistency lots will be produced during the Phase 2 clinical trial
- File the Biologics License Application (BLA) with the FDA
- Six month review of the BLA by the FDA and approval
- Approximate time until FDA approval and Full rate of Production is 5.5 to 6 years

Barr Laboratories

- Fiscal 2001 revenues of $510 Million, Approx 1000 employees
- Manufactures and distributes about 85 pharmaceutical products
- Operations in New York (Headquarters: Pomona, NY), New Jersey and Virginia
- Founded in 1970, but in October 2001 was "re-formed" as the result of a merger between a subsidiary of Barr Laboratories, Inc. and Duramed Pharmaceuticals, Inc
- Originally founded as a generic pharmaceutical company
- Re-focused in 2000 on the following three strategies:
  - development and introduction of proprietary medicines;
  - development and marketing of select off-patent (generic) products; and
  - challenging patents protecting select branded products.
- Currently pursuing proprietary products that are complementary to its therapeutic category focus, including cancer agents; female healthcare products, including hormone replacement and oral contraceptives; and anti-viral products (including Adenovirus vaccine)

Current Issues

- Barr Laboratories Inc. and the previous manufacturer, Wyeth, continue negotiations for the transfer of documents/technologies related to the vaccine.
- Complying with the current environmental standards of using acetone in manufacturing
- Availability of viable cGMP WI-38 human diploid fibroblast cells
- The possibility of BSE contamination of the master seeds from fetal calf serum

Outlook for the Future

- The Department of Defense has taken a wise move by investing money to remanufacture the Adv vaccine
- High ARD rates may continue to plague the services
- The arrival of the Adv vaccines will be a much awaited event and should drastically decrease ARD rates

References

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Institute of Medicine, Urgent Attention Needed to Restore Lapsed Adenovirus Vaccine Availability: A Letter Report Institute of Medicine, Washington, D.C., 2000